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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRADAXA safely and effectively. See full prescribing information for PRADAXA.

PRADAXA® (dabigatran etexilate) capsule for oral use
Initial U.S. Approval: [year]

INDICATIONS AND USAGE

PRADAXA is a direct thrombin inhibitor indicated for

- the prevention of stroke and systemic embolism in patients with non-valvular persistent/persistent, paroxysmal, or permanent atrial fibrillation (1.1)

DOSAGE AND ADMINISTRATION

- Do not open the capsules and do not swallow the pellets outside the capsules (2)
- Recommended Dose: 150 mg taken orally, twice daily (2.1, 2.2)
- In high bleeding risk patients, consider 110 mg taken orally, twice daily (2.3)
- Discontinue Vitamin K antagonists before using dabigatran (2.3.4)
- Switching from or to parenteral anticoagulants requires specific timing (2.3.5)
- Take a missed dose as soon as possible on the same day if 6 hours prior to next scheduled dose. Do not double the daily dose. (2.6.4)
- Surgical interventions may require the temporary discontinuation of dabigatran (2.6.7)
- Patients can stay on dabigatran while being cardioverted (2.8)

DOSAGE FORMS AND STRENGTHS

Capsules 110 mg, 150 mg (3)

CONTRAINDICATIONS

- Active major bleeding or medical conditions associated with an increased risk of bleeding (4.1)
- Severe renal impairment (CrCl <30 mL/min) (4.2)
- Concomitant treatment with systemic ketoconazole (4.3)
- Placement of indwelling spinal or epidural catheter or port and within first hour after removal (4.4)
- Hypersensitivity to dabigatran etexilate (4.5)

WARNINGS AND PRECAUTIONS

- General risk of bleeding (5.1)
- Use caution in conditions with increased risk of hemorrhage (5.2)
- Temporary discontinuations of PRADAXA and increased risk of stroke
- Use caution with P-gp inducers/increased risk of inefficacy (5.3)

ADVERSE REACTIONS

Most common adverse reactions are: bleeding, including life-threatening and fatal bleeding, and dyspepsia or dyspepsia like symptoms (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant treatment with systemic ketoconazole rifampicin (5.4.3, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: [m/year]

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*Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE****1.1 Prevention of Stroke and Systemic Embolism**

PRADAXA is indicated for ~~the prevention~~reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

2 DOSAGE AND ADMINISTRATION

~~Swallow capsule whole. Do not break, chew or empty the contents of the capsule open the capsules and do not swallow the pellets outside the capsule as this could result in excessive exposure.~~ PRADAXA may be administered with or without food [see Clinical Pharmacology (12.3)].

2.1 Prevention of Stroke and Systemic Embolism

The recommended dosage of PRADAXA is 150 mg taken orally, twice daily.

~~2.2~~ 2.2 High Bleeding Risk Patients

~~For those patients with a potentially higher risk of bleeding a PRADAXA dose of 110 mg taken orally, twice daily may be considered. The 110 mg dose was less effective in preventing stroke and systemic emboli and showed only slightly less major bleeding. In general, the 150 mg dose should be used. The 110 mg dose can be considered for patients at higher than usual risk of bleeding, such as those with a history of major bleeds, X, or Y [see Use in Specific Populations (8.7)].~~

2.24 Switching from or to a Vitamin K Antagonist Warfarin

~~In switching patients from currently taking warfarin, a Vitamin K antagonist, start PRADAXA, should only be started after Vitamin K antagonists have been discontinued and after when their international normalized ratio (INR) is below 2.0.~~

~~In patients switching to warfarin, start warfarin 3 days before discontinuing PRADAXA; in patients with moderate renal dysfunction (creatinine clearance [CrCl] 50-80 mL/min) start warfarin 2 days before discontinuing PRADAXA. When the INR is checked at the time of PRADAXA discontinuation, the presence of dabigatran can contribute to an elevation of their INR. Once PRADAXA has been stopped for at least 2 days, the INR will better reflect warfarin's effect.~~

2.35 Switching from or to Parenteral Anticoagulants

~~In patients currently taking a parenteral anticoagulant, PRADAXA should be given 0 to 2 hours prior to the time that the next dose of the alternate therapy would be due or at the time of discontinuation in case of continuous treatment (e.g., intravenous unfractionated heparin [UFH]). In patients currently taking PRADAXA, who do not have severe renal impairment (CrCl <30 mL/min), wait 12 hours after the last dose before switching from PRADAXA initiating treatment with a parenteral anticoagulant. In patients with severe renal impairment, wait 24 hours.~~

2.46 Missed Dose

~~If the prescribed dose of PRADAXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. A dose may be taken up to 6 hours prior to the next scheduled dose. A missed dose should be omitted if it cannot be taken more than at least 6 hours before the next scheduled dose. The dose of dabigatran patient should not take the missed dose by doubling the double daily dose to make up for a missed doses.~~

2.5 Patients with Severe Renal Impairment

The recommended dosage of PRADAXA in patients with severe renal impairment (CrCl <30 mL/min) is 150 mg taken once every other day [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

2.67 Surgery and Interventions

~~Patients on PRADAXA who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of PRADAXA.~~

Preoperative Phase

~~In advance of invasive or surgical procedures including spinal puncture and the placement of a spinal or epidural catheter or port, PRADAXA should be stopped temporarily because of an increased risk of bleeding. If possible, PRADAXA should be discontinued at least 24 hours before invasive or surgical procedures because of an increased risk of bleeding. In high bleeding risk patients [see Use in Specific Populations (8.7)] or in patients undergoing major surgery or spinal puncture or the placement of a spinal or epidural catheter or port in which complete hemostasis may be required consider stopping PRADAXA 12 to 24 days prior to the procedure before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer and this should be considered in advance of any procedures. PRADAXA should be discontinued at least 5 days before invasive surgical procedures in patients with moderate (CrCl between 30 and 50 mL/min) and severe (CrCl < 30 mL/min) renal impairment [see Use in Specific Populations (8.6)].~~

~~PRADAXA should be stopped prior to spinal puncture and the placement of a spinal or epidural catheter or port and within the first hour following removal because of an increase risk of bleeding.~~

~~If surgery cannot be delayed, there may be an increase in the risk of bleeding [see Warnings and Precautions (5.1)]. This risk of bleeding should be weighed against the urgency of intervention. If an acute intervention is required, PRADAXA should be temporarily discontinued. A surgery/intervention should be delayed, if possible, until at least 12 hours after the last dose is taken. If surgery cannot be delayed, there may be an increase in the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.~~

Spinal Anesthesia/Epidural Anesthesia/Lumbar Puncture

~~Procedures such as spinal anesthesia may require complete hemostasis function.~~

~~The risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 1 hour should elapse before the administration of the first dose of PRADAXA. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.~~

Post-Procedural Period

~~Resume treatment as soon as complete hemostasis is achieved. Also Switching from or to Parenteral Anticoagulants (2.4) and Use in Specific Populations (8.8); H. The bleeding risk can be assessed by the Ecarin clotting time (ECT). This test is a better marker of the anticoagulant activity of dabigatran than activated partial thromboplastin time (aPTT), prothrombin time (PT) or INR or thrombin time. If ECT is not available, the aPTT test provides an approximate indication of PRADAXA's anticoagulant activity [see Clinical Pharmacology (12.2)].~~

3 DOSAGE FORMS AND STRENGTHS

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110 mg: A capsule with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted in black with "R110".

150 mg: A capsule with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted in black with "R150".

4 CONTRAINDICATIONS

4.1 Active Bleeding

PRADAXA is contraindicated in patients with active pathological bleeding or medical conditions associated with an increased risk of bleeding [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

4.2 Severe Renal Impairment

PRADAXA is contraindicated in patients with severe renal impairment (CrCl <30 mL/min).

4.3 Concomitant Treatment

PRADAXA is contraindicated in patients being treated concomitantly with systemic ketoconazole.

4.4 Spinal Catheter

PRADAXA is contraindicated during spinal puncture and the placement of a spinal or epidural catheter or port and within the first hour following removal of PRADAXA use in patients undergoing spinal/epidural anesthesia or spinal puncture because of an increase in the risk of bleeding. PRADAXA is contraindicated during the placement of a spinal or epidural catheter or port and within the first hour following removal.

4.5 Hypersensitivity
PRADAXA is contraindicated in patients with known hypersensitivity to dabigatran etexilate (e.g., urticaria, bronchospasm, rash, and pruritus) [see Adverse Reactions (6.1)].

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

PRADAXA can increase the risk of bleeding and cause significant and sometimes fatal bleeding. Major or severe bleeding may occur at any site and regardless of location may lead to disabling, life-threatening or fatal outcomes. In RE-LY, a life threatening bleed (bleeding that was fatal, symptomatic intracranial, or was associated with at least one of the following: reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, hypotension requiring the use of intravenous inotropic agents or the need for surgical intervention) occurred at an annualized rate of 1.5% and 1.9% on PRADAXA 150 mg and warfarin, respectively.

Signs or symptoms of blood loss, for example, a drop in hemoglobin and/or hematocrit or blood pressure hypotension, should lead to further work up and a search for a bleeding site. [see also Contraindications (4.1) and Dosage and Administration (2.2)].

Risk factors for bleeding include:

- Surgery or invasive procedures including such as spinal puncture, arterial puncture and the placement of a spinal or epidural catheter or port [see Dosage and Administration (2.2)].
- The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with PRADAXA. In patients who are bleeding, the aPTT test may be useful to assist in identifying patients with excessive in determining an excess of anticoagulant activity, despite its limited sensitivity to dabigatran etexilate. An aPTT greater than 80 sec is associated with a higher risk of bleeding.

Spinal Anesthesia/Epidural Anesthesia/Lumbar Puncture

Procedures such as spinal anesthesia may require complete hemostasis function.

The risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 1 hour should elapse before the administration of the first dose of PRADAXA. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.

Medications that increase the risk of bleeding

- As an anticoagulant, PRADAXA capsules should be used with caution in conditions with an increased risk of bleeding. Co-administration (e.g., of anti-platelet agents (including aspirin and clopidogrel), heparin, fibrinolytic therapy and chronic use of, and NSAID therapies) is known to increase the risk of bleeding. In RE-LY approximately 40% of patients were using aspirin at baseline [see Adverse Reactions (6) and Clinical Studies (14)].
- Labor and delivery [see Use in Special Populations (8.2)].

Swallowing

The following treatments have not been studied in this patient population and would be expected to increase the risk of bleeding if used concomitantly with PRADAXA capsules: warfarin or vitamin K antagonists, unfractionated heparins (except at doses necessary to maintain a patent central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GpIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, prasugrel, and the P-gp inhibitors itraconazole, tacrolimus, cyclosporine, and ritonavir, nelfinavir, saquinavir and tipranavir.

5.2 Temporary Discontinuations of PRADAXA

Discontinuing anticoagulants, including PRADAXA, for active bleeding, elective surgery or invasive procedures places patients at an increased risk of stroke. Lapses in therapy should be avoided, and if anticoagulation with PRADAXA must be temporarily discontinued because of an adverse event(s), therapy should be restarted as soon as possible.

5.3 Effect of P-gp Inducers and Inhibitors on Exposure

The concomitant use of PRADAXA with P-gp inducers reduces exposure to dabigatran. The P-gp inducer, rifampicin, reduced the exposure to dabigatran by 67% and dose adjustment is needed [see Drug Interactions (7)]. The impact of co-administering other P-gp inducers, e.g. carbamazepine and St. John's Wort, with PRADAXA has not been tested and these should generally be avoided [see Clinical Pharmacology (12.3)].

The effect of some P-gp inhibitors, such as itraconazole and ritonavir, has not been studied [see Clinical Pharmacology (12.3)].

4.4 Spinal Catheter

PRADAXA is contraindicated during spinal puncture and the placement of a spinal or epidural catheter or port and within the first hour following removal because of an increase in the risk of bleeding.

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6 ADVERSE REACTIONS

The following serious adverse reactions are also discussed elsewhere in the labeling:

- Bleeding and bleeding-related events (e.g., anemia, thrombocytopenia) may be caused by PRADAXA, as a consequence of its anticoagulant effect. Major or severe bleeding may occur and regardless of location may lead to disabling, life-threatening or fatal outcomes [see Warnings and Precautions (5.1)].
- Major bleeding incidence was increased approximately 2-fold during concomitant aspirin or clopidogrel use or the combination, and by approximately 50% with concomitant NSAID use in treatment groups [see Table xx and Warnings and Precautions (5.2)].
- Hypersensitivity [see Contraindications (4.5)].

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Table xx. Yearly rate of major bleeds by medication use in RE-LY

Concomitant medication use	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Aspirin			
— 0% (never)	2.1	2.4	2.6
— 0% < and < 50%	4.5	5.9	5.2
— 50% < and < 100%	7.6	7.7	10.5
Clopidogrel			
— 0% (never)	2.7	3.1	3.2
— 0% < and < 50%	6.1	6.9	6.3
— 50% < and < 100%	8.4	8.1	11.6
Aspirin + Clopidogrel			
— 0% (never)	2.7	3.2	3.4
— 0% < and < 50%	7.2	6.8	6.6
— 50% < and < 100%	6.1	6.9	7.6
Cox II inhibitor			
— 0% (never)	2.8	3.3	3.5
— 0% < and < 50%	6.1	6.4	8.0
— 50% < and < 100%	14.0	3.4	5.2

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Because clinical studies are conducted under widely varying conditions and over varying lengths of time, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

Safety in patients with non-valvular atrial fibrillation with another risk factor for stroke was evaluated in a randomized comparison of two doses of PRADAXA and warfarin (an open-label warfarin study, RE-LY, [Randomized Evaluation of Long-term anticoagulant therapy]). In this study, in which 5,983 patients were treated with two doses (PRADAXA 110 mg BID and 6,059 patients were treated with PRADAXA 150 mg BID) of PRADAXA were compared with open-label warfarin for a mean of 21 months in the RE-LY study (Randomized Evaluation of Long-term anticoagulant therapy) (4,936 patients were treated with PRADAXA 110 mg BID, and 4,939 patients were treated with PRADAXA 150 mg BID for more than 1 year and 2,387 patients were treated with PRADAXA 110 mg BID, and 2,405 patients were treated with PRADAXA 150 mg BID for more than 2 years), the Phase III trial in the prevention of thromboembolic stroke and systemic embolism in more than 18,000 in patients with atrial fibrillation patients with a median duration of 20 months [see Clinical Studies (14)].

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Drug Discontinuation in RE-LY

Over the course of the trial, the total rate of patients with adverse events leading to treatment discontinuation was 19% for PRADAXA 110 mg, 21.0.5% for PRADAXA 150 mg and 165.7% for warfarin. The most frequent adverse events for PRADAXA leading to discontinuation were gastrointestinal events. The most frequent gastrointestinal event leading to discontinuation was dyspepsia, nausea and upper abdominal pain [2.2% of patients] and it was not dose related (approximately 1% of subjects discontinued in each dabigatran arm). Other gastrointestinal events that resulted in a higher proportion of discontinuations in dabigatran treated subjects compared to warfarin treated patients included gastrointestinal hemorrhage, nausea, upper abdominal pain, and diarrhea.

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Commented [A7]: SPONSOR – Please check %.

Bleeding [see Warnings and Precautions (5)] Table xx. Adverse events leading to treatment discontinuation reported in ≥ 0.5% of subjects in RE-LY

Preferred term	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Number of subjects	5983 (100.0)	6059 (100.0)	5998 (100.0)
Total with AEs leading to treatment discontinuation	1138 (19.0)	1242 (20.5)	939 (15.6)
Anaemia	43 (0.7)	61 (1.0)	39 (0.7)
Gastrointestinal haemorrhage	39 (0.7)	55 (0.9)	37 (0.6)
Dyspnoea	37 (0.6)	43 (0.7)	33 (0.6)
Fall	14 (0.2)	18 (0.3)	32 (0.5)
INR increased	2 (0.0)	3 (0.0)	29 (0.5)
Hematuria	27 (0.5)	36 (0.6)	26 (0.4)
Cardiac failure congestive	29 (0.5)	20 (0.3)	26 (0.4)
Pneumonia	33 (0.6)	24 (0.4)	22 (0.4)
Chest pain	17 (0.3)	29 (0.5)	21 (0.4)
Nausea	41 (0.7)	42 (0.7)	20 (0.3)
Diarrhoea	36 (0.6)	36 (0.6)	20 (0.3)
Renal failure acute	30 (0.5)	21 (0.3)	18 (0.3)
Rectal haemorrhage	20 (0.3)	29 (0.5)	15 (0.3)
Dizziness	32 (0.5)	27 (0.4)	13 (0.2)
Renal failure	27 (0.5)	26 (0.4)	12 (0.2)
Abdominal pain upper	31 (0.5)	36 (0.6)	7 (0.1)
Dyspepsia	57 (1.0)	57 (0.9)	2 (0.0)

Percentages were calculated using total number of subjects per treatment as the denominator.
MedDRA Version 12.0

RE-LY Bleeding Definitions

In the RE-LY study, bleeding was classified as major according to the following guidelines:

Major bleeding fulfilled one or more of the following criteria:

— Bleeding associated with a reduction in hemoglobin of at least 20 grams per deciliter or leading to a transfusion of at least 2 units of blood or packed cells; 50 grams per deciliter; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

Bleeding

Table 1 shows the number of patients experiencing ~~serious major and total~~ bleeding event rates during the treatment period in the RE-LY study, with the annualized bleeding rate in (%). Major bleeds fulfilled one or more of the following criteria: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding). A life threatening bleed event was defined as bleeding that was fatal, symptomatic intracranial, or was associated with at least one of the following: reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, hypotension requiring the use of intravenous inotropic agents or the need for surgical intervention. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid and subdural bleeds. Major bleeding on both PRADAXA doses were associated with a lower yearly event rate for major bleeds, minor bleeds and any bleeds as compared with warfarin treatment. Subjects randomized to PRADAXA 110 mg BID had a significantly lower risk for major bleeds compared with warfarin (hazard ratio (95% CI) 0.80 (0.70, 0.93) (p=0.0026)). The rate of major bleeding events on PRADAXA 150 mg BID was similar to warfarin. In Table 1, the category of major bleeds includes both life-threatening bleeds and a sub-category of major bleeds and non-life-threatening bleeds. Intracranial bleeds are a sub-category of life-threatening bleeds. Intracranial bleeds hemorrhage includes intracerebral (hemorrhagic stroke), subarachnoid and subdural bleeds. For this reason, these events may be counted in multiple categories.

Table 1 Frequency and Annualized Event Rate (%) of Major and Other Bleeding Events

	PRADAXA 110 mg BID N (%)	PRADAXA 150 mg BID N (%)	Warfarin N (%)
Number of subjects randomized	6015	6076	6022
Subject years	11899	12033	11794
Major bleeds*	342 (2.987)	399 (3.32)	424 (3.657)
Hazard ratio vs warfarin (95% CI)	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	
p-value	0.0026	0.3146	
Life threatening bleed*MBEs	147 (1.24)	179 (1.549)	218 (1.985)
Hazard ratio vs warfarin (95% CI)	0.67 (0.54, 0.82)	0.80 (0.66, 0.98)	
p-value	0.0001	0.0305	
Intracranial hemorrhage*CH	27 (0.23)	38 (0.32)	90 (0.876)
Hazard ratio vs warfarin (95% CI)	0.30 (0.19, 0.45)	0.41 (0.28, 0.60)	
p-value	<0.0001	<0.0001	
Investigator reported Any bleeds*	1754 (14.74)	1993 (16.56)	2166 (18.437)
Hazard ratio vs warfarin (95% CI)	0.78 (0.73, 0.83)	0.91 (0.85, 0.96)	
p-value	<0.0001	0.0016	

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	PRADAXA 150 mg BID N (%)	Warfarin N (%)
Number of randomized patients	6076	6022
Patient-years	12033	11794
Major bleeds*	399 (3.3%)	421 (3.6%)
Hazard ratio vs. warfarin (95% CI)	0.93 (0.81, 1.07)	
p-value	0.3	
Life threatening MBEs bleed*	179 (1.5)	218 (1.8)
Hazard ratio vs. warfarin (95% CI)	0.80 (0.66, 0.98)	
p-value	0.03	
ICH Intracranial hemorrhage	38 (0.3)	90 (0.8)
Hazard ratio vs. warfarin (95% CI)	0.41 (0.28, 0.60)	
p-value	<0.0001	
Any bleed (investigator reported)†	1993 (16.6)	2166 (18.4)
Hazard ratio vs. warfarin (95% CI)	0.91 (0.85, 0.96)	
p-value	0.002	

*Adjudicated

Events may be counted in multiple categories. †Bleeds

ICH consists of adjudicated hemorrhagic stroke and subdural and/or subarachnoid hemorrhage.

†Investigator reported bleeding events

PRADAXA treatment resulted in a higher rate incidence of major gastrointestinal bleeds on PRADAXA 150 mg compared to warfarin (4.14% 150 mg, 1.657% vs. 150 mg; 1.107% warfarin, respectively) and any gastrointestinal bleeds (5.41% 150 mg, 6.13% 150 mg, and 4.02% warfarin, respectively) compared to warfarin.

The risk of major bleeding with PRADAXA 150 mg compared to warfarin was consistent across all major subgroups of patients (by baseline characteristics) (Figure 1) with the exception of age, body mass index (BMI), region, and diabetes with age ≥ 65 years with diabetes or hypertension (Figure 1). There was a higher risk of bleeding with PRADAXA 150 mg in patients ≥ 75 years of age. Though renal function has an important role in the relationship between age and risk of major bleed, it appears that increasing age, independent of renal function is associated with a trend for greater risk of a major bleed on dabigatran relative to warfarin. As BMI increased, there was an increased trend for more major bleeding on PRADAXA 150 mg relative to warfarin. There was less major bleeding on PRADAXA compared to warfarin in subjects in Asia compared to other regions of the world. Diabetic subjects aged ≥ 65 years showed a trend for more major bleeding on dabigatran relative to warfarin compared to subjects that were not diabetic and aged ≥ 65 years.

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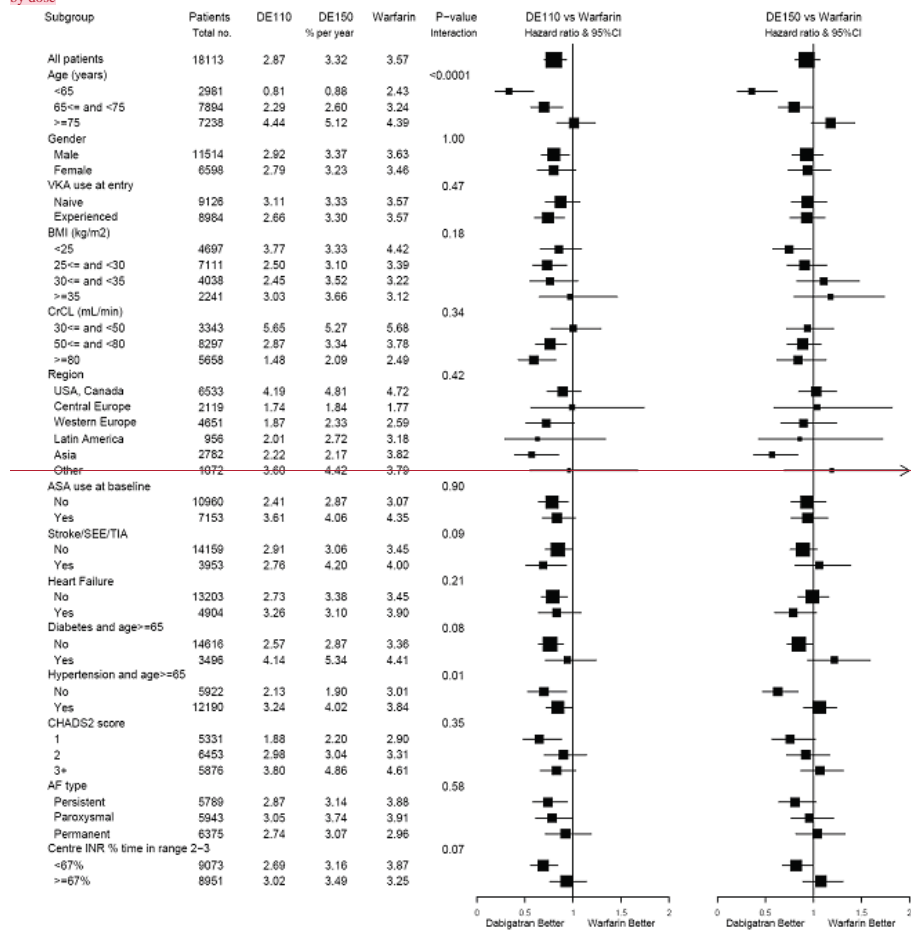
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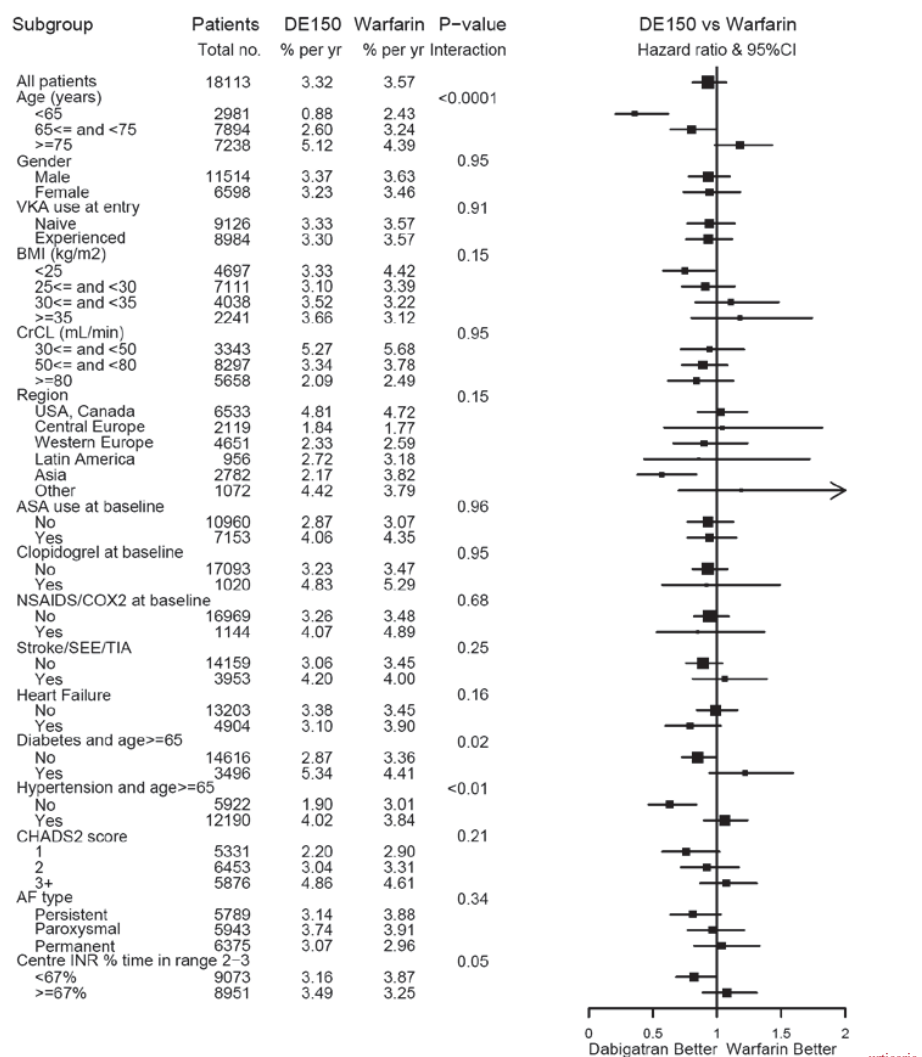
A small number of subjects (< 0.1%) treated with PRADAXA 110 mg and 150 mg had reports of dFigure 1: Baseline characteristics across subgroups for major bleeds by dose



Allergic reactions or drug hypersensitivity, allergic edema, including anaphylactic reaction, and anaphylactic shock. Figure 1: Forest plot for major bleeds with PRADAXA 150mg vs. warfarin in various patient subgroups

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bronchospasm, rash and pruritus have been reported in patients who received PRADAXA.

A small number of subjects (< 0.1%) treated with PRADAXA 110 mg and 150 mg had reports of drug hypersensitivity, allergic edema, anaphylactic reaction, and anaphylactic shock.

Gastrointestinal (GI)/Dyspepsia in RE-LY

PRADAXA subjects had an increased incidence of GI adverse events (AEs) (34.6%, 34.5%, and 24.1% for PRADAXA 110 mg, PRADAXA 150 mg, and warfarin, respectively). Additional GI events that were reported more frequently with PRADAXA treatment included upper abdominal pain, gastritis, abdominal discomfort, gastroesophageal reflux disease, dysphagia, and flatulence (Table 2). There was no consistent dose-response relationship with respect to GI AEs.

Table 2 — Number (%) of Treated Subjects with Dyspepsia and Gastritis-like Symptoms (Safety Set) Liver Function Tests in RE-LY

In the RE-LY study, potential abnormalities of transaminases and bilirubin/liver-function tests (LFT) on PRADAXA occurred at a rate similar to the rate in with a comparable or lower incidence in PRADAXA vs warfarin-treated patients (Table 3).

Table 3 — Summary of Abnormal Liver Function Tests, Number (%) of Subjects (Safety Set)

LFT elevation	PRADAXA 110 mg BID N (%)	PRADAXA 150 mg BID N (%)	Warfarin N (%)
Total treated	5983	6059	5998
ALT or AST > 3xULN	118 (2.0)	106 (1.7)	125 (2.1)
ALT or AST > 5xULN	36 (0.6)	45 (0.7)	50 (0.8)
ALT or AST > 3xULN + Bilirubin > 2xULN	11 (0.2)	14 (0.2)	21 (0.4)

Subjects were counted in each category if the respective abnormal LFT event occurred between first dose of study medication and study termination visit.

Overview of Adverse Events/Reactions from RE-LY

The incidence of serious adverse event/reactions and adverse event/reactions was similar across treatment groups. The incidence of AEs was similar between subjects treated with PRADAXA 110 mg BID and PRADAXA 150 mg BID (78.6% and 78.3%, respectively) vs 75.9% of subjects treated with warfarin. The incidence of serious adverse events was similar across treatment groups. However, PRADAXA subjects had a lower incidence of fatal AEs, life-threatening AEs, and events that required hospitalization as compared to warfarin subjects.

Adverse events classified by system organ class and preferred terms reported $\geq 5\%$ from any treatment group of the RE-LY study are shown in Table 4 below. The observed incidences of adverse events for PRADAXA were in the range of warfarin. Diarrhea, dyspepsia, and nausea were the most frequently reported GI AEs, all of which were reported at a higher frequency with PRADAXA 110 mg and PRADAXA 150 mg treatment, particularly for dyspepsia (6.2%, 5.7%, and 1.4% for PRADAXA 110 mg, PRADAXA 150 mg, and warfarin, respectively).

Table 3a: Subjects on PRADAXA 150 mg had an increased incidence of GI adverse events (AEs) (34.5% and 24.1% for PRADAXA 150 mg and warfarin, respectively). Dyspepsia and gastritis-like symptoms were more common in subject/patients on PRADAXA 150 mg compared to warfarin (Table 2).

Table 2 — Number (%) of Treated Subject/Patients with Dyspepsia and Gastritis-like Symptoms

	PRADAXA 150 mg BID N (%)	Warfarin N (%)
Number of subjects	6059	5998
Total with dyspepsia/gastritis	940 (15.5)	470 (7.8)
Dyspepsia*	738 (12.2)	354 (5.9)
Gastritis-like symptoms ^{a,b}	257 (4.2)	142 (2.4)

Percentages were calculated using total number of subject/patients per treatment as the denominator.

*Dyspepsia includes dyspepsia, abdominal pain upper, abdominal pain, abdominal discomfort, epigastric discomfort.

**Gastritis-like includes gastritis, GERD, esophagitis, gastritis erosive, gastric hemorrhage, gastritis hemorrhagic, hemorrhagic erosive gastritis.

^a Represents a composite of sponsor-identified AEs (preferred terms) that were similar and likely reporting the same subject.

Table 4 — Adverse Events Reported in at Least 5.0% of Subjects in PRADAXA Arms (Safety Set)

System Organ Class/ Preferred term	PRADAXA 110 mg BID N (%)	PRADAXA 150 mg BID N (%)	Warfarin N (%)
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System Organ Class/ Preferred term	PRADAXA 110 mg BID N(%)	PRADAXA 150 mg BID N(%)	Warfarin N(%)
Dyspnea	498 (8.3)	526 (8.7)	551 (9.2)
Dizziness	457 (7.6)	458 (7.6)	554 (9.2)
Edema-peripheral	446 (7.5)	442 (7.3)	453 (7.6)
Fatigue	370 (6.2)	367 (6.1)	353 (5.9)
Diarrhea	355 (5.9)	367 (6.1)	328 (5.5)
Chest pain	287 (4.8)	355 (5.9)	342 (5.7)
Dyspepsia	368 (6.2)	345 (5.7)	83 (1.4)
Atrial fibrillation	303 (5.1)	313 (5.2)	327 (5.5)
Arthralgia	248 (4.1)	313 (5.2)	329 (5.5)
Cough	320 (5.3)	310 (5.1)	346 (5.8)
Nasopharyngitis	315 (5.3)	309 (5.1)	327 (5.5)
System Organ Class/ Preferred term	PRADAXA 150 mg BID N(%)	Warfarin N(%)	
Dyspnea	526 (8.7)	551 (9.2)	
Dizziness	458 (7.6)	554 (9.2)	
Edema-peripheral	442 (7.3)	453 (7.6)	
Fatigue	367 (6.1)	353 (5.9)	
Diarrhea	367 (6.1)	328 (5.5)	
Chest pain	355 (5.9)	342 (5.7)	
Dyspepsia	345 (5.7)	83 (1.4)	
Atrial fibrillation	313 (5.2)	327 (5.5)	
Arthralgia	313 (5.2)	329 (5.5)	
Cough	310 (5.1)	346 (5.8)	
Nasopharyngitis	309 (5.1)	327 (5.5)	

Percentages were calculated using total number of subjects per treatment as the denominator.

7 DRUG INTERACTIONS

See *Clinical Pharmacology* (12.3)

Rifampicin

When co-administering PRADAXA with rifampicin the dose of PRADAXA should be adjusted. If PRADAXA is initiated in patients on rifampicin, the dose of PRADAXA should be increased to 450 mg BID.

If rifampicin is initiated in patients on PRADAXA the dose adjustment should be gradual. The maintenance dose of PRADAXA following initiation of rifampicin should be continued on Days 1 and 2, increased to 300 mg BID on Days 3-5, and further increased to 450 mg BID on Day 6 and thereafter.

Dose reduction of PRADAXA after stopping the treatment with rifampicin should be gradual. The maintenance dose of PRADAXA after cessation of the treatment with rifampicin should be maintained on Days 1 and 2, reduced initially to 300 mg BID on Days 3-5, and then further reduced to 150 mg BID on Day 6 and thereafter [see *Warnings and Precautions* (5.3) and *Clinical Pharmacology* (12.3)].

Ketoconazole
Systemic ketoconazole increased total dabigatran AUC₀₋₂₄ and C_{max} values by 138% and 135%, respectively, after a single dose of 400 mg, and 153% and 149%, respectively, after multiple dosing of 400 mg ketoconazole QD. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole [see *Contraindications* (4.3) and *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

PRADAXA has been shown to decrease the number of implantations, decrease the number of viable fetuses/implantations when male and female rats were treated at a dosage of 70 mg/kg, and increase the number of dead offspring when given at doses of 70 mg/kg (about 2.6 to 3.0 times the human exposure at MRHD of 300 mg/day based on AUC comparisons) to female rats. Although PRADAXA did not induce major malformations in rats or rabbits, it did increase the incidences of fetal skeletal variations related to delayed or irregular ossification of skull bones and vertebrae in rats (about 2.6 to 3.0 times the human exposure at MRHD of 300 mg/day based on AUC comparisons) prior to mating and up to implantation (gestation day 6). Treatment of pregnant rats after implantation with PRADAXA at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at MRHD of 300 mg/day based on AUC comparisons) increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Although PRADAXA increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat, it did not induce major malformations in rats or rabbits.

8.2 Labor and Delivery

Safety and effectiveness of PRADAXA during labor and delivery have not been studied in clinical trials established.

Death of offspring and mother rats PRADAXA resulted in delayed labor and deaths of some rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation day 7) to weaning (when given at doses of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300

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mg/day based on AUC comparisons) to pregnant female rats from implantation (gestation day 7) to weaning (lactation day 21) with PRADAXA at a dosage of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons).

8.3 Nursing Mothers

It is not known whether PRADAXA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRADAXA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of PRADAXA in pediatric patients has not been established.

8.5 Geriatric Use

Of the total number of subjects-patients in the RE-LY study, 82% were 65 and over, while 40% were 75 and over. The risk of bleeding increased with advancing age in all treatment groups. The relative risk of major bleeding may be greater for PRADAXA 150 mg BID compared to warfarin increased in patients ≥ 75 years of age (Figure 1). PRADAXA is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function and anti-coagulant activity.

8.6 Renal Impairment

The AUC of dabigatran after the oral administration of dabigatran etexilate is approximately 2.7-7 timesfold higher in volunteers with moderate renal insufficiency (CrCl between 30 to 50 mL/min) than in those without renal insufficiency. In a small number of volunteers with severe renal insufficiency (CrCl < 30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than observed in a population without renal insufficiency [see Contraindications (4.2) and Clinical Pharmacology (12.3)].

Table 5 Terminal Half-life of Total Dabigatran in Healthy Subjects and Subjects with Impaired Renal Function

Glomerular filtration rate (CrCl) (mL/min)	Median half-life (gCV%, range) (h)
≥ 80	13 (26%; 11-23)
≥ 50 – < 80	15 (43%; 12-34)
≥ 30 – < 50	18 (19%; 13-23)
< 30	27 (15%; 22-35)

8.7 High Bleeding Risk Patients

For those patients with a potentially higher risk of bleeding, (e.g., age ≥ 75 years, CHADS₂ score of ≥ 3 , moderate renal impairment (30 to 50 mL CrCl/min), concomitant treatment with P-gp inhibitors, or previous gastrointestinal bleed), a reduced dose of 110 mg twice daily may be considered [see Dosage and Administration (2.3)].

8.8 Cardioversion

A total of 1255 subjects had cardioversions performed during the RE-LY study, 409 (6.8%), 415 (6.8%) and 431 (7.2%) in the PRADAXA 110 mg, PRADAXA 150 mg and warfarin treatment groups respectively. The rate of stroke occurring within 30 days of cardioversion was low and similar across all treatment groups [PRADAXA 110 mg (0.03%), PRADAXA 150 mg (0.03%) and warfarin (0.02%)].

8.9 Hepatic Insufficiency

Hepatic patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥ 2 ULN, or hepatitis A, B or C were excluded in clinical trials.

8.10 Body Weight

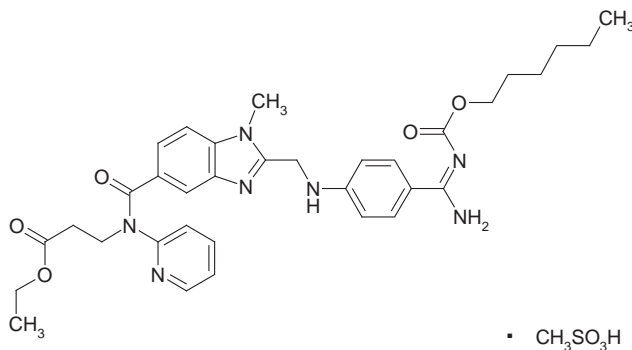
The dabigatran trough concentrations were approximately 20% lower in patients with a BW of ≥ 100 kg compared with those with a BW of 50 to 100 kg. The majority (80.8%) of the subjects were in the BW of ≥ 50 kg and < 100 kg category with no clear difference detected. Limited data in patients with a BW of ≤ 50 kg are available.

10 OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. There is no antidote to dabigatran etexilate or dabigatran. In the event of hemorrhagic complications appropriate clinical support should be initiated, treatment with PRADAXA must be discontinued and the source of bleeding investigated. Dabigatran is primarily excreted in the urine therefore adequate diuresis must be maintained. Surgical hemostasis or the transfusion of fresh frozen plasma or RBCs may be considered. While dabigatran can be dialyzed (protein binding is low), there is limited clinical experience to demonstrate the utility of this approach in clinical studies with the removal of about 60% of drug over 2-3 hours; however, the amount of data supporting this approach is limited clinical experience to demonstrate the utility of this approach in clinical studies. Surgical hemostasis or the transfusion of fresh frozen plasma or RBCs may be considered. There is some experimental evidence to support the role of activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but however their usefulness in clinical settings has not yet been systematically demonstrated established. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. Measurement of aPTT or ECT may help guide therapy dabigatran's anticoagulant effect may also be considered [see Dosage and Administration (2) and Clinical Pharmacology (12.2)]. All symptomatic treatment can be given.

11 DESCRIPTION

The chemical name for dabigatran etexilate mesylate is: β -Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino] iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-ethyl ester, methanesulfonate. The empirical formula is $C_{34}H_{41}N_7O_5 \cdot CH_3O_3S$ and the molecular weight is 723.86 (mesylate salt), 627.75 (free base). The structural formula is:



Dabigatran etexilate mesylate is a yellow-white to yellow powder. A saturated solution in pure water has a solubility of 1.8 mg/mL. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol.

Each The capsule for oral administration contains ~~126.83 mg or~~ 172.95 mg dabigatran etexilate mesylate, which is equivalent to ~~440 mg or~~ 150 mg, ~~respectively,~~ of dabigatran etexilate and the following inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shells ~~is~~ are composed of carageenan, FD&C Blue No. 2, FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dabigatran etexilate is a pro drug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase catalyzed hydrolysis in plasma and in the liver. Dabigatran and its acyl glucuronides are a potent, competitive, direct thrombin inhibitors and is the main active component in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

12.2 Pharmacodynamics

At recommended therapeutic doses, dabigatran etexilate prolongs the aPTT, ECT, and thrombin time (TT). The most sensitive measure of response to dabigatran was TT; however, the most common measure is aPTT. With an oral dose of 150 mg BID the median peak aPTT is approximately 2x control. Twelve hours after the last dose the median aPTT is 1.5x control, with less than 10% of patients exceeding 2x control. In the RE-LY trial, the median (10th – 90th percentile) trough aPTT in patients receiving the 150 mg dose was 51.9 [40.3 – 76.4] seconds. The INR test is relatively insensitive to the activity of dabigatran and may or may not be elevated in patients on dabigatran etexilate. In transition of dabigatran etexilate to warfarin therapy, the INR is unlikely to be interpretable.

Cardiac Electrophysiology

No prolongation of the QTc interval was observed with dabigatran etexilate at doses up to 600 mg.

12.3 Pharmacokinetics

Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester and the ester is promptly removed forming dabigatran, the active agent. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Pharmacokinetics described here refer to the sum of dabigatran and its glucuronides. Dabigatran displays dose proportional pharmacokinetics in healthy subjects and patients in the range of doses from 10 to 400 mg.

Absorption

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate ~~is~~ was approximately 3 to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. After oral administration of dabigatran etexilate in healthy volunteers, there is a pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in the plasma concentrations with C_{max} attained within 0.5 and 2.0 at 1 hours post administration in the fasted state. Co-administration of dabigatran etexilate with a high-fat meal delayed the time to peak plasma concentration C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran etexilate; dabigatran etexilate may be administered with or without food.

A study evaluating post-operative absorption of dabigatran etexilate, 1 to 3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a flat plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration in a post-operative period because of contributing factors such as anesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. It was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after drug administration. Postoperative patients show a delayed absorption and lower bioavailability due to low gastric motility and coadministration of opioids with a geometric mean C_{max} of dabigatran attained 6 h instead of 2 h post-dose as in controls. The absorption of dabigatran normalized ≥ 24 hours post-surgery.

The oral bioavailability of dabigatran etexilate ~~may be increased~~ by 75/40% compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. The integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate.

Distribution

Dabigatran is about 35% bound to Low (34% to 35%) concentration independent binding of dabigatran to human plasma proteins was observed. The red blood cell to plasma partitioning of dabigatran measured as total radioactivity is less than 0.3. The volume of distribution of dabigatran of 60 to 70 L is 50-70 L. Dabigatran pharmacokinetics exceeded the volume of total body water indicating moderate tissue distribution of dabigatran. C_{max} and the area under the plasma concentration-time curve ~~are~~ were dose proportional after single doses of 10–400 mg. Given BID, dabigatran's accumulation factor is approximately two.

Elimination

After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85%). Renal clearance of dabigatran is 80% of total clearance after intravenous administration. The recovery of radioactivity in urine and feces after oral administration is 7% and 86% of the administered dose, respectively. The half-life of dabigatran in healthy subjects is 12 to 17 hours. Fecal excretion accounted for 6% of the administered dose. Recovery of the total radioactivity ranged from 88 to 94% of the administered dose by 168 hours post dose. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

The half-life is 10.7 h and 11.2 h in healthy elderly (≥ 65 years) male and female volunteers, respectively. The half-life is prolonged to 15.3 h and 18.4 h in patients with mild or moderate renal impairment, respectively.

Metabolism

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor or inducer of CYP450 enzymes. Dabigatran is subject to conjugation forming pharmacologically active acyl glucuronides. Four positional isomers, 1-O, 2-O, 3-O and 4-O-acylglucuronide exist, and each accounts for less than 10% of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods.

Specific Populations

Renal Impairment

An open, parallel-group single center study compared PRADAXA pharmacokinetics and pharmacodynamics in groups of subjects with different degrees of renal function (mild, moderate, severe impairment [150 mg single dose] and patients on dialysis [50 mg single dose] vs. healthy subjects). Exposure to dabigatran increases with the severity of renal function impairment.

Pharmacokinetic parameters of dabigatran in otherwise healthy subjects compared to subjects with normal renal function (Table X).

Table X. Pharmacokinetic Parameters of Dabigatran in Healthy Subjects

Renal Function	Creatinine clearance (mL/min)	Mean fold increase in AUC following dabigatran 150 mg BID	Mean fold increase in C_{max} following dabigatran 150 mg BID	Median half-life (t _{1/2} , hr)	Wash-out time to reach pharmacologically ineffective concentration (~20 ng/mL), hr (days)†
Normal	$CrCl \geq 80$	1 x	1 x	13	20 (0.8)
Mild	$50 \leq CrCl < 80$	1.5 x	1.1 x	15	52 (2.2)
Moderate	$30 \leq CrCl < 50$	3.2 x	1.7 x	18	76 (3.2)
Severe	$CrCl < 30$	6.3 x	2.1 x	27	100 (4.2)

*Following 150 mg BID dose

† Following 150 mg every other day

A similar finding was observed in RE-LY trial where patients with mild, moderate and severe renal impairment had 1.5x (N = 3745), 2.3x (N = 1443) and 3.3x (N = 19) higher pre-dose dabigatran concentration compared to patients with normal creatinine clearance (≥ 80 mL/min; N = 2573).

No dose adjustment of PRADAXA is recommended in patients with mild and moderate renal impairment based on efficacy and bleeding risk findings in RE-LY (see Adverse Events (6.1) & Clinical Studies (14)). PRADAXA dose should be adjusted to 150 mg every other day in subjects with severe renal impairment. Computer-based simulations were used to derive the dosing regimen in patients with severe renal impairment by matching the exposure to that seen in RE-LY trial. Dosing recommendations for patients on dialysis cannot be provided.

Hepatic Impairment

Administration of dabigatran etexilate in patients with moderate hepatic impairment (Child-Pugh B) showed a large inter-subject variability, but no evidence of a systematic, unidirectional change in exposure or pharmacodynamics (see Use in Special Populations (8.9)).

Drug Interactions

In vitro assessment of drug interactions

Dabigatran etexilate is a substrate of P-gp. Dabigatran etexilate and dabigatran are not metabolized by the cytochrome P450 system and had no effects *in vitro* on human cytochrome P450 enzymes. Therefore interactions with other drugs that utilize these pathways are unlikely and dabigatran are not metabolized by the cytochrome P450 system and had no effects *in vitro* on human cytochrome P450 enzymes. Therefore interactions with other drugs that utilize these pathways are unlikely.

In vivo assessment of drug interactions

In clinical studies exploring CYP3A4, CYP2C9, and P-gp pathways, dabigatran etexilate did not meaningfully alter the pharmacokinetics of amiodarone, atorvastatin, diclofenac, digoxin, pantoprazole, and ranitidine.

In the RE-LY study, dabigatran plasma samples were also collected. Trough plasma concentrations with the concomitant use of PPIs, amiodarone, verapamil, digoxin and H2 antagonists and digoxin did not appreciably change the concentration of dabigatran and were not associated with any increased risk of bleeding.

The effects of the following P-gp inhibitors on dabigatran's pharmacokinetics are listed for reference with dabigatran etexilate below:

Ketoconazole:

Systemic ketoconazole increased total dabigatran AUC_{0-∞} and C_{max} values by 138% and 135%, respectively, after a single dose of 400 mg, and 153% and 149%, respectively, after multiple dosing of 400 mg ketoconazole QD. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole (see Contraindications (4.3) and Drug Interactions (7)).

Verapamil:

When dabigatran etexilate was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased. The extent of increase depending on the formulation of verapamil and timing of administration, and formulation of verapamil. If verapamil is present in the gut when dabigatran is taken it will increase exposure to dabigatran with the greatest increase observed when a single dose of immediate-release verapamil was given one hour prior to dabigatran (AUC increased

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by a factor of 2.4). If verapamil is given two hours after dabigatran, the increase in AUC is negligible. In the population pharmacokinetics study from RE-LY, in patients administered verapamil no important changes in dabigatran trough levels were observed.

Amiodarone:

When dabigatran etexilate was co-administered with a single 600 mg oral dose of amiodarone, the dabigatran AUC and C_{max} increased by 58% and 50%, respectively. The increase in exposure was mitigated by a 65% increase in the renal clearance of dabigatran in the presence of amiodarone. It should be noted that the increase in renal clearance will persist after amiodarone is discontinued because of amiodarone's long half-life. In addition, plasma samples were also collected in the RE-LY study [see Clinical Studies (14)]. Trough plasma concentrations were approximately 13.3% higher with no increased risk of bleeding seen. In the population pharmacokinetics study from RE-LY, in patients administered amiodarone no important changes in dabigatran trough levels were observed.

Quinidine:

Study 1: Dabigatran etexilate was given 1 hour after a single oral dose of 600 mg quinidine sulfate. Dabigatran AUC and C_{max} were increased by approximately 100% in an inter-individual group comparison. Subjects experienced adverse events and the study was prematurely terminated.

Study 2: Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1000 mg. Dabigatran etexilate was given over 3 consecutive days, the last evening dose on day 3 with or without quinidine pre-dosing. Dabigatran AUC and C_{max} were increased on average by 53% and 56%, respectively with concomitant quinidine.

Clopidogrel:

When dabigatran etexilate was given concomitantly with a loading dose of 300 mg or 600 mg clopidogrel, the dabigatran AUC and C_{max} increased by approximately 30% to 40% respectively. The concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. The coagulation measures for dabigatran effect, aPTT, ECT or TT, or the inhibition of platelet aggregation (IPA) as measurements of clopidogrel effect remained unchanged when comparing combined treatment and the respective mono-treatments.

In the studies with the P-gp inhibitors ketoconazole, amiodarone, verapamil, quinidine, clopidogrel and enoxaparin the time to peak, terminal half-life and mean residence time of dabigatran were not affected [see Warnings and Precautions (5.3) and Drug Interactions (7)].

Rifampicin:

Pre-dosing of rifampicin at a dose of 600 mg QD for 7 days decreased dabigatran AUC and C_{max} by 66% and 67%, respectively. The effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability exposure was observed after another 7 days [see Warnings and Precautions (5.3)].

Concomitantly administered clarithromycin, atorvastatin, diclofenac, ranitidine and digoxin had no impact on dabigatran. Enoxaparin 40 mg given s.c. for 3 days with the last dose given 24 hours before a single dose of PRADAXA had no impact on the exposure to dabigatran or the coagulation measures aPTT, ECT or TT.

-Impact of PRADAXA on other Drugs

In clinical studies exploring CYP3A4, CYP2C9, and P-gp pathways, dabigatran etexilate did not meaningfully alter the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole, or ranitidine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dabigatran was not carcinogenic when administered by oral gavage to mice and rats for up to 2 years. The highest doses tested (200 mg/kg/day) in mice and rats were approximately 3.6 and 6 times, respectively, the human exposure at MRHD of 300 mg/day based on AUC comparisons).

Dabigatran was not mutagenic in *in vitro* tests, including bacterial reversion tests, mouse lymphoma assay and chromosomal aberration assay in human lymphocytes, and the *in vivo* micronucleus assay in rats.

In the rat fertility study with oral gavage doses of 15, 70, and 200 mg/kg, males were treated for 29 days prior to mating, during mating (max. 20 days), up to scheduled termination (approximately 7 weeks total) and females were treated 15 days prior to mating through gestation Day 6. No adverse effects on male or female fertility were observed at 200 mg/kg or 9 to 12 times the human exposure at MRHD of 300 mg/day based on AUC comparisons. However, the number of implantations decreased in females receiving 70 mg/kg or 3 times the human exposure at MRHD of 300 mg/day based on AUC comparisons.

14 CLINICAL STUDIES

The clinical evidence for the efficacy of PRADAXA is derived from the RE-LY study (Randomized Evaluation of Long-term anticoagulant therapy) a multi-center, multi-national, randomized parallel group study comparing two blinded doses of PRADAXA (110 mg BID and 150 mg BID) with open-label warfarin in patients with non-valvular persistent, paroxysmal, or permanent atrial fibrillation and one of the following additional risk factors:

- Previous stroke, transient ischemic attack (TIA), or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure, ≥ New York Heart Association NYHA-Class 2
- Age ≥75 years
- Age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

at moderate-to-high risk of stroke or systemic embolism.

The primary objective of this study was to determine if PRADAXA was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke (ischemic and hemorrhagic) and systemic embolic events (SEE). The study was designed to ensure that dabigatran preserved more than 50% of warfarin's effect as established by previous randomized, placebo-controlled trials of warfarin in atrial fibrillation. Statistical superiority was also analyzed.

A In the RE-LY study, a total of 18,113 patients were randomized and followed for a median of 2 years. The with a mean age was of 71.5 years and the mean CHADS₂ score was of 2.1. The population had approximately equal proportions of patients with CHADS₂ score 1, 2 and ≥3. The patient population was 64% male, 70% Caucasian, and 16% Asian and 1% black. Twenty percent of subjects/patients had a history of a stroke or TIA and 50% were VKA naïve, defined as less than 2 months total life time exposure to a Vitamin K antagonist (VKA). Thirty-two percent of the population had never been exposed to a VKA. RE-LY had a median treatment exposure of 20 months with PRADAXA given as fixed dose without coagulation monitoring. In addition to documented non-valvular atrial fibrillation (AF) e.g., persistent AF or paroxysmal, patients had one of the following additional risk factors for stroke:

- Previous stroke, transient ischemic attack, or systemic embolism
- Left ventricular ejection fraction <40%

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- Symptomatic heart failure, \geq NYHA Class 2
- Age \geq 75 years
- Age \geq 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and coronary artery disease (CAD) 28%. At baseline, 39% of subject patients were on Fifty percent of the patient population was VKA naïve defined as less than 2 months total life time exposure. Thirty-two percent of the population had never been exposed to a VKA. For those patients randomized to warfarin, the median time in therapeutic range (INR 2 to 3) for the trial was 67%. Concomitant medications included aspirin (25% of subjects used at least 50% of the time in study), and 6% were on clopidogrel (3.6%), aspirin + clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%), statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%), and. The mean time in therapeutic range (INR 2-3) in subjects randomized to warfarin was 64%; the mean time INR measurements were greater than 4 or less than 1.5 was 2% and 5%, respectively. proton pump inhibitors (17.8%).

For the primary endpoint, stroke and systemic embolism, no subgroups (i.e., age, weight, gender, renal function, ethnicity, etc.) were identified with a different risk ratio compared to warfarin. PRADAXA 110 mg was non-inferior to warfarin and PRADAXA 150 mg was statistically significantly superior to warfarin and to PRADAXA 110 mg in reducing the risk of stroke and/or SEE (see Table 6 and Figure 2).

Table 6 First Occurrence of Stroke or Systemic Embolism (Primary Endpoint) in the RE-LY Study

	PRADAXA 150 mg BID	Warfarin*
Patients randomized	6076	6022
Stroke and/or Systemic Embolism		
Incidences (%)	134 (2.2%)	202 (3.4%)
Hazard ratio vs. warfarin (95% CI)	0.65 (0.52, 0.81)	
p-value for superiority	p = 0.0001	

*dosed to target INR of 2 to 3

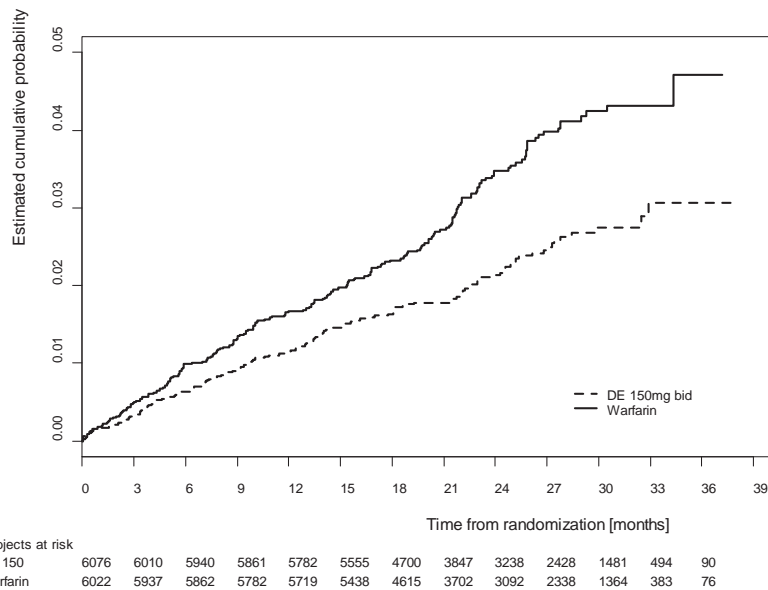
The upper bound of the 95% confidence interval for non-inferiority based on the log of the risk ratio for dabigatran vs. warfarin was 1.38.

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Figure 2: Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism

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The contribution of the components of the composite endpoint, including categories of stroke by subtype, is shown outlined in Table 7. The treatment effect was driven primarily by a reduction in stroke. For the individual components of the primary endpoint stroke, ischemic stroke, and hemorrhagic stroke, PRADAXA 150 mg BID was statistically significantly superior to warfarin for both ischemic and hemorrhagic stroke prevention. PRADAXA 110 mg was comparable to warfarin for the endpoints of stroke and ischemic stroke and superior to warfarin for hemorrhagic stroke.

Table 7 First Occurrence of Ischemic or Hemorrhagic Strokes in the RE-LY Study

	PRADAXA 150 mg BID	Warfarin
Subjects randomized	6076	6022
Stroke		
Incidence (%)	122 (1.01)	186 (1.58)
Hazard ratio vs. warfarin (95% CI)	0.64 (0.51, 0.81)	
p-value	0.0001	
Systemic Embolism		
Incidence (%)	13 (0.11)	21 (0.18)
Hazard ratio vs. warfarin (95% CI)	0.61 (0.30, 1.21)	
p-value	0.16	
Ischemic stroke		
Incidence (%)	103 (0.86)	134 (1.14)
Hazard ratio vs. warfarin (95% CI)	0.75 (0.58, 0.97)	
p-value	0.03	
Hemorrhagic stroke		
Incidence (%)	12 (0.10)	45 (0.38)
Hazard ratio vs. warfarin (95% CI)	0.26 (0.14, 0.49)	
p-value	<0.001	

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Both PRADAXA doses reduced all cause mortality and vascular mortality and the reductions associated with 150 mg were statistically superior to warfarin for vascular death (Table 8).

Table 8 Mortality in the RE-LY Study

	<u>PRADAXA 150 mg BID</u>	<u>Warfarin</u>
Subjects randomized	6076	6022
All-cause mortality		
Incidence (%)	438 (3.64)	487 (4.13)
Hazard ratio vs warfarin (95% CI)	0.88 (0.77, 1.00)	
p-value	0.0517	
Vascular mortality		
Incidence (%)	274 (2.28)	317 (2.69)
Hazard ratio vs warfarin (95% CI)	0.85 (0.72, 0.99)	
p-value	0.0430	

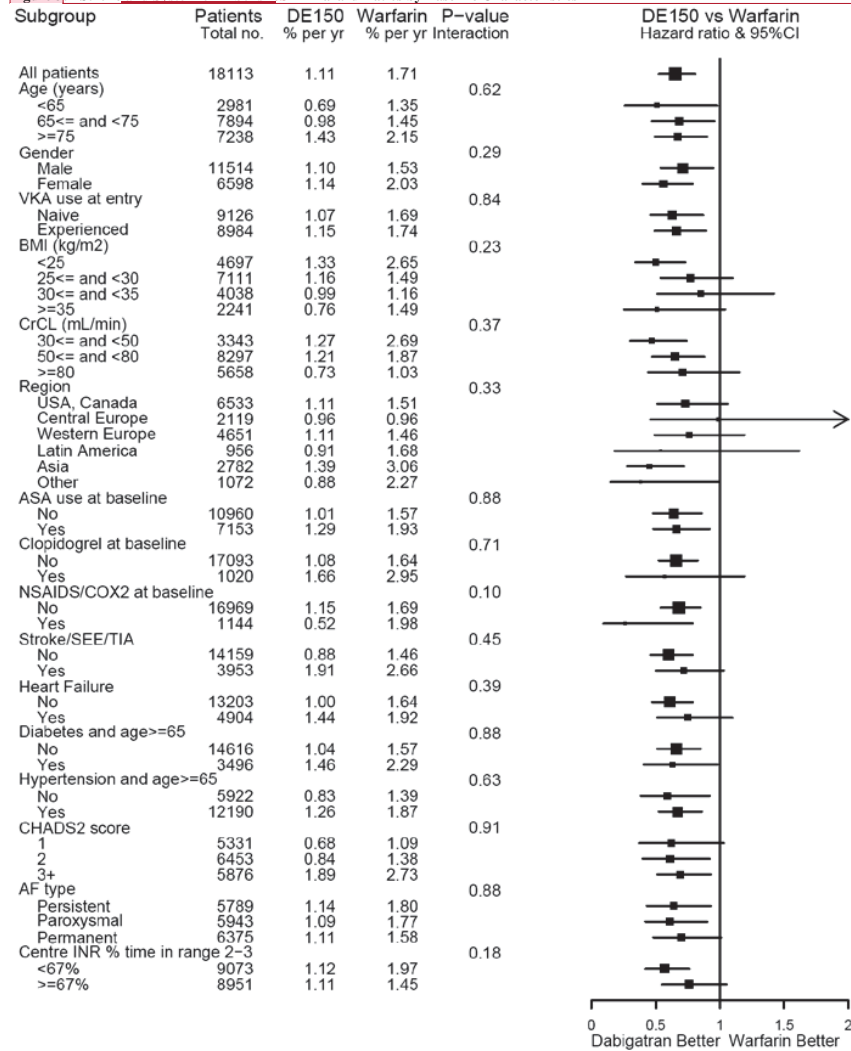
% refers to yearly event rate

	<u>PRADAXA 110 mg BID</u>	<u>PRADAXA 150 mg BID</u>	<u>Warfarin</u>
Subjects randomized	6015	6076	6022
All-cause mortality			
Incidence (%)	446 (3.75)	438 (3.64)	487 (4.13)
Hazard ratio vs warfarin (95% CI)	0.91 (0.80, 1.03)	0.88 (0.77, 1.00)	
p-value	0.1308	0.0517	
Vascular mortality			
Incidence (%)	289 (2.43)	274 (2.28)	317 (2.69)
Hazard ratio vs warfarin (95% CI)	0.90 (0.77, 1.06)	0.85 (0.72, 0.99)	
p-value	0.2084	0.0430	

% refers to yearly event rate

The efficacy of PRADAXA 110 mg and 150 mg BID was generally consistent across all major subgroups (Figure 3). There were too few African-American, black, and Hispanic patients to adequately assess the differences in effects in those populations.

Figure 3: Stroke and Systemic Embolism/SEE Hazard Ratios by Baseline Characteristics



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Efficacy findings for stroke, all-cause mortality and major bleeds are shown by center level INR control in Table 8. The advantage of PRADAXA 150 mg relative to warfarin was most apparent in patients enrolled at centers with INR control below the median. The level of INR control in warfarin-treated subjects as reflected in these center-level analyses.

Table 8 Center-level analysis Mortality in the RE-LY Study

	Centers with INR control below the median	Centers with INR control above the median
Stroke/Systemic Embolism ^{SEE}		
HR	0.57	0.77
95% CI	0.42, 0.76	0.56, 1.06
p-value	0.0002	0.10
All-cause mortality		
HR	0.78	1.01
95% CI	0.66, 0.93	0.84, 1.23
p-value	0.007	0.89
Major Bleed		
HR	0.82	1.08
95% CI	0.68, 0.99	0.89, 1.31
p-value	0.04	0.45

Median center level time in therapeutic range = 67%

A variety of additional outcomes were examined in the RE-LY study. Two composite endpoints were prespecified as secondary endpoints in RE-LY and are shown along with their components in e net clinical benefit as measured by the composite clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction (MI), all cause deaths, and major bleeds was assessed and is presented as part of Table 9. The yearly event rates for hazard ratio for each of the composite endpoints suggests favorable effects of PRADAXA groups were lower. PRADAXA 150 mg compared relative to the warfarin group. The risk reduction for this composite endpoint was 8% and 10% for the PRADAXA 110 mg BID and 150 mg BID treatment groups. The absolute risk of myocardial infarction (MI) (including silent MI) was low (0.83% to 0.81%/year) but was greater on PRADAXA (relative risk 1.29 for PRADAXA 110 mg vs warfarin and 1.32 for PRADAXA 150 mg vs warfarin). Other components evaluated included all hospitalizations which had statistically significant fewer hospitalizations at PRADAXA 110 mg BID compared to warfarin (7% risk reduction, 95% CI 0.87, 0.99, p=0.021).

Table 9 Other Measures Evaluated

	PRADAXA 150 mg BID	Warfarin
Patients randomized	6076	6022
Composite endpoints		
vascular 8474609Pulmonary embolism		
Incidence (%)	18 (0.245)	12 (0.10)
Hazard ratio vs. Warfarin (95% CI)	1.47 (0.71, 3.06)	
Myocardial infarction*		
Incidence (%)	89 (0.797) (0.81)	66 (0.575) (0.64)
Hazard ratio vs. Warfarin (95% CI)	1.32 (0.96, 1.81) (1.27 (0.94, 1.71))	
0.09All-cause mortality		
Incidence (%)	438 (3.6)	487 (4.1)
Hazard ratio vs warfarin (95% CI)	0.88 (0.77, 1.00)	
p-value	0.0517	
Vascular mortality		
Incidence (%)	274 (2.3)	317 (2.7)
Hazard ratio vs warfarin (95% CI)	0.85 (0.72, 0.99)	
p-value	0.0430	

% refers to yearly event rate

*Myocardial infarction included silent MI

16 HOW SUPPLIED/STORAGE AND HANDLING

PRADAXA 110 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted with "R110". The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0108-54 Unit of use bottle of 60 capsules
- NDC 0597-0108-60 Blister package containing 60 capsules (10 x 6 capsule blister cards) (hospital unit dose pack)

PRADAXA 150 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted with "R150". The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0135-54 Unit of use bottle of 60 capsules
- NDC 0597-0135-60 Blister package containing 60 capsules (10 x 6 capsule blister cards) (hospital unit dose pack)

Storage

Bottles:

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Once opened, the product must be used within 30 days. Keep the bottle tightly closed. Store in the original package in order to protect from moisture.

Blisters:

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store in the original package in order to protect from moisture.

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Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 Benefits and Risks

- Summarize the effectiveness and potential side effects of PRADAXA.
- Tell patients to take PRADAXA exactly as prescribed by their health care provider.
- Remind patients not to discontinue PRADAXA without first discussing it with the health care provider who prescribed it.
- Patients should be advised not to chew the capsules before swallowing and not to open the capsules and take the pellets alone (e.g., sprinkled over food or into beverages).
- Recommend that patients read the Medication Guide.

17.2 Bleeding

Inform patients that they may bleed more easily, may bleed longer, and should call their health care provider for any signs or symptoms of bleeding.

17.3 Other Signs and Symptoms Requiring Medical Attention

Instruct patients to seek emergency care right away if they have any of the following, which may be a sign or symptom of serious bleeding:

- Unusual bruising (bruises that appear without known cause or that get bigger)
- Pink or brown urine
- Red or black, tarry stools
- Coughing up blood
- Vomiting blood, or vomit that looks like coffee grounds

Instruct patients to call their health care provider or to get prompt medical attention if they experience any signs or symptoms of bleeding:

- Pain, swelling or discomfort in a joint
- Headaches, dizziness, or weakness
- Reoccurring nose bleeds
- Unusual bleeding from gums
- Bleeding from a cut that takes a long time to stop
- Menstrual bleeding or vaginal bleeding that is heavier than normal

Instruct patients to call their health care provider if they experience any signs or symptoms of dyspepsia or dyspepsia like symptoms:

- Dyspepsia (upset stomach), burning, or nausea
- Abdominal pain or discomfort
- Epigastric discomfort, GERD (gastric indigestion)

17.4 Invasive or Surgical Procedures

Patients should inform their health care provider that they are taking PRADAXA before any invasive procedure is scheduled.

17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so their health care provider knows about other treatments that may affect bleeding risk (e.g., aspirin or NSAIDs).

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Rev: May 2010

Resource number here
Component number here

MEDICATION GUIDE**PRADAXA (pra dax' a)
(dabigatran etexilate)
capsules**

Read this Medication Guide before you start taking PRADAXA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about PRADAXA?

- PRADAXA lowers your chance of having a stroke or other serious problems caused by a blood clot. But, PRADAXA can cause bleeding which can be serious, and sometimes lead to death. This is because PRADAXA is a blood thinner that stops clots from forming.
- **Do not take PRADAXA if you:**
 - Are currently bleeding or have medical conditions that increase your risk of bleeding
 - Have serious kidney problems
 - Are taking the anti-fungal drug ketoconazole (Nizoral®) by mouth
 - Are allergic to dabigatran etexilate or any of the other ingredients listed at the end of this Medication Guide

PRADAXA may need to be stopped one or more days before any surgery or medical/dental procedure. Talk to the doctor who prescribed PRADAXA for you to find out when you need to stop taking PRADAXA.

- **You may have a higher risk of bleeding if you take PRADAXA and:**
 - Are over 75 years old
 - Have kidney problems
 - Have stomach or intestine bleeding that is recent or keeps coming back, or you have a stomach ulcer
 - Take other medicines that increase your risk of bleeding, including:
 - aspirin or aspirin containing products
 - non-steroidal anti-inflammatory drugs (NSAIDs). This includes prescription and non-prescription brands, such as, but not limited to, ibuprofen (Advil®, Motrin®), naproxen (Aleve®, Naprosyn®) or Celebrex.
 - clopidogrel (Plavix®)

Ask your doctor if you are not sure if the medicine you take increases your risk of bleeding.

Call your doctor right away or seek emergency treatment if you have any of these signs or symptoms of bleeding:

- Unexpected bleeding or bleeding that lasts a long time
- Bleeding that is severe or you cannot control
- Pink or brown urine
- Red or black stools (looks like tar)
- Bruises that happen without a known cause or get larger
- Cough up blood or blood clots
- Vomit blood or your vomit looks like “coffee grounds”
- Unexpected pain, swelling, or joint pain
- Headaches, feeling dizzy or weak

Do not stop taking PRADAXA without first talking to the doctor who prescribes it for you because stopping it may increase your risk of a stroke. See “What are the possible side effects of PRADAXA?” for more information about side effects.

What is PRADAXA?

- PRADAXA is a prescription medicine used to treat people with a medical condition known as atrial fibrillation. With atrial fibrillation, part of the heart doesn't beat the way it should. This can lead to clots forming and increasing the risk of a stroke. PRADAXA is a blood thinner that stops clots from forming and reduces the risk of a stroke from occurring.

What should I tell my doctor before taking PRADAXA?

- PRADAXA may not be right for you. Before taking PRADAXA, tell your doctor about all of your medical conditions, including if you:
 - Have kidney problems
 - Have ever had bleeding problems
 - Have ever had stomach ulcers
 - Are pregnant or plan to become pregnant. It is not known if PRADAXA will harm your baby.

- Are breast-feeding. It is not known if PRADAXA passes into breast milk. You and your doctor should decide if you should take PRADAXA and breast-feed.

Tell all of your doctors and dentists that you are taking PRADAXA. They should talk to the doctor who prescribed PRADAXA for you, before you have **any** surgery or medical/dental procedure.

Tell your doctor about all the medicines you take, including:

- All prescription and over-the-counter (OTC) medicines, vitamins, and herbal supplements. Some of your other medicines or herbal supplements may affect the way PRADAXA works. Certain medicines may increase your risk of bleeding. See “What is the most important information I should know about PRADAXA?”
- Medicines that increase your risk of bleeding, such as:
 - Blood thinners (warfarin or Coumadin[®])
 - Medicines that contain heparin (enoxaparin)
 - Aspirin or aspirin containing products
 - Non-steroidal anti-inflammatory drugs (NSAIDs). This includes prescription and non-prescription brands, such as, but not limited to, ibuprofen (Advil[®], Motrin[®]), naproxen (Aleve[®], Naprosyn[®]) or Celebrex[®].
 - Clopidogrel (Plavix[®])

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine, or any time you go to the doctor or pick up a prescription.

While taking PRADAXA, do not start, stop, or change any medicine without first talking with your doctor.

Tell your doctor if you are allergic to any medicines.

How should I take PRADAXA?

- Take PRADAXA exactly as prescribed by your doctor.
- Do not take PRADAXA more often than your doctor tells you to.
- Take PRADAXA by mouth, two times each day.
- You can take PRADAXA with or without food.
- Swallow the capsules whole. Do not open the capsules. Do not empty the pellets from the capsule.
- If you miss a dose of PRADAXA, take it as soon as you remember. If your next dose is less than 6 hours away, skip the missed dose. Do not take two doses of PRADAXA at the same time.
- Your doctor will decide how long you should take PRADAXA. Do not stop taking PRADAXA without first talking with your doctor.
- If you plan to have surgery or a dental procedure, tell your doctor and dentist that you are taking PRADAXA. You may have to stop taking PRADAXA for a short time.
- If you take too much PRADAXA, go to the nearest hospital emergency room or call your doctor or the Poison Control Center right away.

What should I avoid while taking PRADAXA?

- Avoid activities that can cause a serious injury. Call your doctor right away if you fall or injure yourself.

What are the possible side effects of PRADAXA?

- PRADAXA can cause serious side effects including allergic reactions and bleeding leading to hospitalization or death.
- Common side effects of PRADAXA include stomach pain or burning; difficulty breathing; feeling dizzy or lightheaded; swelling in your hands, feet, or face; feeling tired; diarrhea; chest pain or pressure in your chest; pain in your joints; cough; runny nose or irritated throat.

This is not a complete list of side effects and should not take the place of talking with your doctor. Your doctor or pharmacist can give you more information about the possible side effects of this drug. Talk to your doctor if you have questions about any side effects that bother you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088, or by visiting www.fda.gov/medwatch.

How should I store PRADAXA?

- Store PRADAXA at room temperature [77°F or 25°C].
- Short-term storage at higher or lower temperatures [from 59°F (15°C) to 86°F (30°C)] is acceptable.
- Store PRADAXA in the original package to protect it from moisture.
- Keep PRADAXA and all medicines out of the reach of children.

Other information about PRADAXA

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PRADAXA for a condition for which it was not prescribed.
- Do not give your PRADAXA to other people, even if they have similar symptoms. It may hurt them.
- This Medication Guide is a summary of the most important information about PRADAXA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about PRADAXA that is written for health professionals.
- For more information, call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906.

What are the ingredients in PRADAXA?

Active ingredient: dabigatran etexilate mesylate

Inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shells are composed of carageenan, FD&C Blue No. 2, FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink.

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